RISK FACTORS AND OUTCOMES OF CARBAPENEM-RESISTANT GRAM NEGATIVE BLOODSTREAM INFECTION IN INTENSIVE CARE UNIT, HUSM

BY

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ABBREVIATIONS

APACHE	Acute Physiology and Chronic Health Evaluation
BSI	Blood Stream Infection
CLD	Chronic Liver Disease
COAD	Chronic Obstructive airway Disease
CR	Carbapenem-Resistant
CRE	Carbapenem Resistant Enterobacteriaciae
CS	Carbapenem-Sensitive
CVA	Cerebrovascular accident
DM	Diabetes Mellitus
ESBL	Extended Spectrum B-lactamase
EVD	Extra Ventricular Device
GNB	Gram-negative Bacilli
HPT	Hypertension
ICU	Intensive Care Unit
KPC	*K. pneumoniae* Carbapenemase
LOS	Length of stay
MDR	Multidrug-resistant

MDROs	Multidrug-resistant Organisms
MIC	Minimum Inhibitory Concentration
PDR	Pandrug-resistant
SSI	Surgical Site Infection
TPN	Total Parenteral Nutrition
UTI	Urinary Tract Infection
VAP	Ventilator-associated Pneumonia
XDR	Extensively drug-resistant

ABSTRAK

FAKTOR RISIKO DAN HASIL AKIBAT JANGKITAN KUMAN GRAM NEGATIF DALAM DARAH YANG RESISTAN CARBAPENEM DI UNIT RAWATAN RAPI (ICU), HUSM

Objektif : Jangkitan kuman gram negatif semakin berleluasa dan amat membimbangkan. Penyelidikan ini dijalankan bertujuan untuk mengenalpasti faktor risiko dan juga hasil akibat jangkitan kuman Gram negatif di dalam darah pesakit-pesakit ICU, Hospital Universiti Sains Malaysia (HUSM).

Metodologi : Retrospektif, dijalankan secara perbandingan "case-control". Faktor risiko terhadap jangkitan kuman Gram negatif dikenalpasti dengan membandingkan dua kumpulan pesakit : kumpulan pertama (control) terdiri daripada kes yang mempunyai jangkitan kuman Gram negatif yang sensitive kepada Carbapenem dan kumpulan kedua (case) pula terdiri daripada kes yang resistan. Kedua-dua kumpulan ini adalah kes yang dirawat di ICU dalam tempoh yang sama dan memenuhi syarat-syarat kriteria yang diperlukan. 96 sample tersebut telah dipilih secara rawak dan rekod perubatan kes-kes ini dilihat kembali. Data demografik, sejarah penyakit dahulu, penggunaan antibiotik, keputusan mikrobiologi dan hasilnya dicatat.

Keputusan : Daripada 96 sampel yang dikaji, sebanyak 48 kes yang resistan telah dibandingkan dengan 48 kes yang sensitif terhadap Carbapenem. Antara faktor risiko yang dikenalpasti menyebabkan jangkitan kuman Gram negatif di dalam darah yang resistan terhadap Carbapenem, berdasarkan analisis 'Multiple Logistic Regression'

adalah tempoh rawatan di ICU (OR 2.09, 95 % CI 1.01–33.18, p=0.019), adanya penyakit Diabetes Mellitus (OR 3.5, 95 % CI 1.61–13.24, p =0.016), pesakit yang mempunyai tiub trakeostomi (OR 5.17, 95% CI 1.94 – 18.92, p=0.010) dan tiub aliran cecair paru-paru (chest drain) (OR 5.79, 95% CI, 4.27 – 24.40, p = 0.016), sejarah penggunaan Carbapenem (OR 5.90, 95% CI, 4.63 – 7.40, p= 0.002) dan pesakit yang dijangkiti oleh kuman *Acinetobacter baumannii* (OR 6.18, 95% CI, 2.56 – 8.68, p = 0.010) dan juga *Pseudomonas aeruginosa* (OR 4.29, 95% CI, 0.22 – 8.48, p = 0.034).

Secara amnya, jumlah kematian di dalam kumpulan pertama (control) adalah lebih tinggi berbanding dengan kumpulan kedua (case). Walaubagaimana pun, bukti ini secara statistiknya kurang meyakinkan (p = 0.679).

Kematian langsung yang berpunca daripada jangkitan kuman Gram negatif resistan Carbapenem adalah lebih tinggi (24 pesakit) berbanding kumpulan yang sensitive Carbapenem (17 pesakit) (p=0.011).

Kesimpulan : Penyelidikan ini menjelaskan kepentingan pencegahan jangkitan kuman Gram negatif yang resistan dan kebijaksanaan dalam penggunaan antibiotic untuk mengurangkan kematian langsung.

ABSTRACT

RISK FACTORS AND OUTCOMES OF CARBAPENEM-RESISTANT GRAM-NEGATIVE BLOOD STREAM INFECTION IN INTENSIVE CARE UNIT, HUSM

Objectives: Carbapenem-resistant (CR) Gram-negative pathogens have increased substantially and is worrisome. This study was performed to identify the risk factors for development as well as outcomes of CR Gram-negative bacteremia (GNB) among patients in Intensive Care Unit (ICU), Hospital Universiti Sains Malaysia (HUSM).

Methods: Retrospective, case-control study; risk factors for development of CR-GNB were investigated using two groups of patients: the first group (control) consisted of patients who acquired carbapenem susceptible (CS) GNB and the second group (case) included patients with CRGNB. The case groups were compared to the control group defined as patients hospitalized in the ICU during the same period, with similar inclusion and exclusion criterias. 96 cases of Gram-negative bacilli BSI from ICU were randomly selected and their medical record were traced from Record Office and reviewed. Their demographic profiles, underlying diseases, potential risk factors, antibiotic usage, microbiology results and outcome were reviewed.

Results: Total 96 patients were included for the study, 48 patients with CR- were compared to 48 patients with CS-GNB. Increased length of ICU stay (OR 2.09, 95 % CI 1.01–33.18, p=0.019), DM (OR 3.5, 95 % CI 1.61–13.24, p =0.016), presence of tracheostomy and chest drain (OR 5.17, 95% CI 1.94 – 18.92, p=0.010) and (OR 5.79,

95% CI, 4.27 – 24.40, p = 0.016) respectively, prior exposure to carbapenems (OR 5.90, 95% CI, 4.63 – 7.40, p= 0.002) and those who have infected by Acinetobacter baumannii (OR 6.18, 95% CI, 2.56 – 8.68, p = 0.010) and Pseudomonas aeruginosa (OR 4.29, 95% CI, 0.22 – 8.48, p = 0.034) were independent risk factors associated with CR-GNB.

Crude mortality in CS-GNB was greater compared to CR group, however, statistically not significant (p = 0.679). Meanwhile, the attributable mortality in CR-GNB was noted higher than CS-GNB (24 patients in CR compared to 17 patients in CS-GNB), with p=0.011.

Conclusions: This study indicates the importance of preventing CR-GNB blood stream infections and the appropriate use of antimicrobial agents to reduce attributable mortality.

ABSTRACT

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CHAPTER 1

1.0 INTRODUCTION

The prevalence of Gram-negative bacterial pathogens which are resistant to multiple antimicrobial agents is rising in hospitals, and exclusively in intensive care unit (ICU) settings (Rahal, 2009). Livermore and Woodford (2006) stated that the growing prevalence of infections caused by multidrug-resistant *Pseudomonas aeruginosa, Acinetobacter baumannii,* and *Klebsiella pneumoniae* has directed to a major medical problem globally.

Carbapenems, such as meropenem and imipenem, are currently considered to be the ideal means for the management of severe bacterial infections produced by multidrug-resistant Gram-negative pathogens, mostly *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and nonfermenters, i.e., *Acinetobacter baumannii* (Paterson, 2006).

However, the emergence of carbapenem resistance among Gram-negative pathogens has been more and more reported worldwide and is a matter of great concern, ever since it complicates both empirical and guided treatment. Moreover, carbapenem resistance is also associated with additional mechanisms of resistance to other antibiotic classes (Grundmann *et al.*, 2010). This was proven by a study done by Routsi *et al.* (2013) stated an increased rate of carbapenem resistant (CR) *A. baumannii* isolates was detected.

This study is conducted to identify characteristics of patients who developed Carbapenem - Resistant Gram - negative bacteremia (GNB) in the intensive care unit (ICU), Hospital Universiti Sains Malaysia (HUSM), risk factors for acquisition of it, and outcomes of getting Carbapenem - Resistant Gram – negative bacilli infections. Such knowledge should be useful to identify patients at risk, so that they receive in time a targeted antimicrobial therapy.

There have been many studies regarding Carbapenem - resistant (CR) and multidrug - resistant (MDR) gram negative bacilli (GNB) worldwide. The study by Routsi *et al.,* (2013), University of Athens, Greece stated that Carbapenem- susceptible (CS) GNB were most common due *to A. baumanni* (57.2%) and *K. pneumoniae* (25%). Carbapenem-resistant GNB were most common due to *A. baumannii* (37.6%) and *P. aeroginosa* (36.5%). Respiratory tract infection was the most common source in both Carbapenem – susceptible (CS) and Carbapenem-resistant (CR) gram – negative bacilli (GNB), observed in 45% and in 47% patients respectively, followed by other sources in 19% and 13% patients respectively. However, the result of the studies might not represent our local situation since there are very large differences among hospitals, setting, regions or countries.

Data issued in 2004 from the United State National Nasocomial Infection Surveillance System (NNIS) report resistant rates among *P.aeruginosa* isolates to imipenem and quinolones at 21.1% and 29.5% respectively; in intensive care unit (ICU) isolates, the respective rates of resistance were even higher (up to 51.6% for

ciprofloxacin, 31.4% for piperacillin/tazobactam, 38% for imipenem and 23.6% for ceftazidime).

Relevant figures for ICU isolates of *Pseudomonas aeruginosa* adopted from Europe are even worse, as from 1990 through to 1999 resistance to aminoglycosides reached 37% – 70%, to ceftazidime 57%, to piperacillin/tazobactam 53%, to ciprofloxacin 56% and to imipenem 52% (Rossolini *et al.*, 2007).

Multidrug - resistant (MDR) *A.baumannii* isolates are becoming one of the supreme serious therapeutic problems worldwide. Data from the NNIS indicate that from 1986 to 2003, among *Acinetobacter* organisms causing pneumonia in ICUs, resistance to imipenem had increased from 0% to 42% and to ceftazidime from 18% to 68%. The significant rise in the incidence of *A. baumannii* among nosocomial pathogens has explained this microorganism as an unarguable indicator of poor clinical outcomes. (McDonald, 2006) and (Abbo *et al.*, 2007).

1.1 RATIONALE OF STUDY

It is hoped that the results will help clinician to gain :

- Better knowledge and understanding regarding the risk factors of developing Carbapenem – resistant gram - negative bacilli blood - stream infection and outcomes of patients in our local situation since there are very large variations among regions, countries, hospitals or settings.

- Knowledge of the patient characteristics associated with Carbapenem - resistant gram - negative bacilli blood - stream infection will help in recognizing them and avoid further complications.

- Increase awareness of treatment failure and early consideration of salvage antibiotics such as polymyxin B and colistin may potentially lead to improve outcomes.

CHAPTER 2

2.0 LITERATURE REVIEW

2.1 INFECTION

Infection is defined as invasions and multiplication of microorganisms (bacteria, virus, fungi and/or parasites) in body tissues, causing local cellular injury due to competitive metabolism, toxins, intracellular replication, or antigen-antibody response (Dorland, 2007).

It is caused by microbes as below :

- Bacteria like Gram-positive bacteria (*Staphylococci, Streptococci*) and Gram-negative bacteria(*E-coli, Pseudomonas aeruginosa and Klebsiella pneumoniae*)
- Viruses, like virus influenzae or HIV
- Fungi, like one-cell yeasts *Candida species* or *Aspergillus*
- One-cell parasites (protozoa) like *Giardia* or *Entameba histolytica (Modric, 2009)*

The route of infection can be via :

- **airborne infection :**
    - one that is contracted by inhalation of microorganisms or spores suspended in air on water droplets or dust particles.

- **droplet infection :**
    - infection due to inhalation of respiratory pathogens suspended on liquid particles exhaled by someone already infected *(droplet nuclei)* .

- **endogenous infection :**
    - that due to reactivation of organisms present in a dormant focus, as occurs in tuberculosis, etc.

- **tunnel infection :**
    - subcutaneous infection of an artificial passage into the body that has been kept patent.

- **opportunistic infection :**
    - infection by an organism that does not normally cause disease but becomes pathogenic under certain environments (e.g., diminished immune responses) (Dorland, 2007)

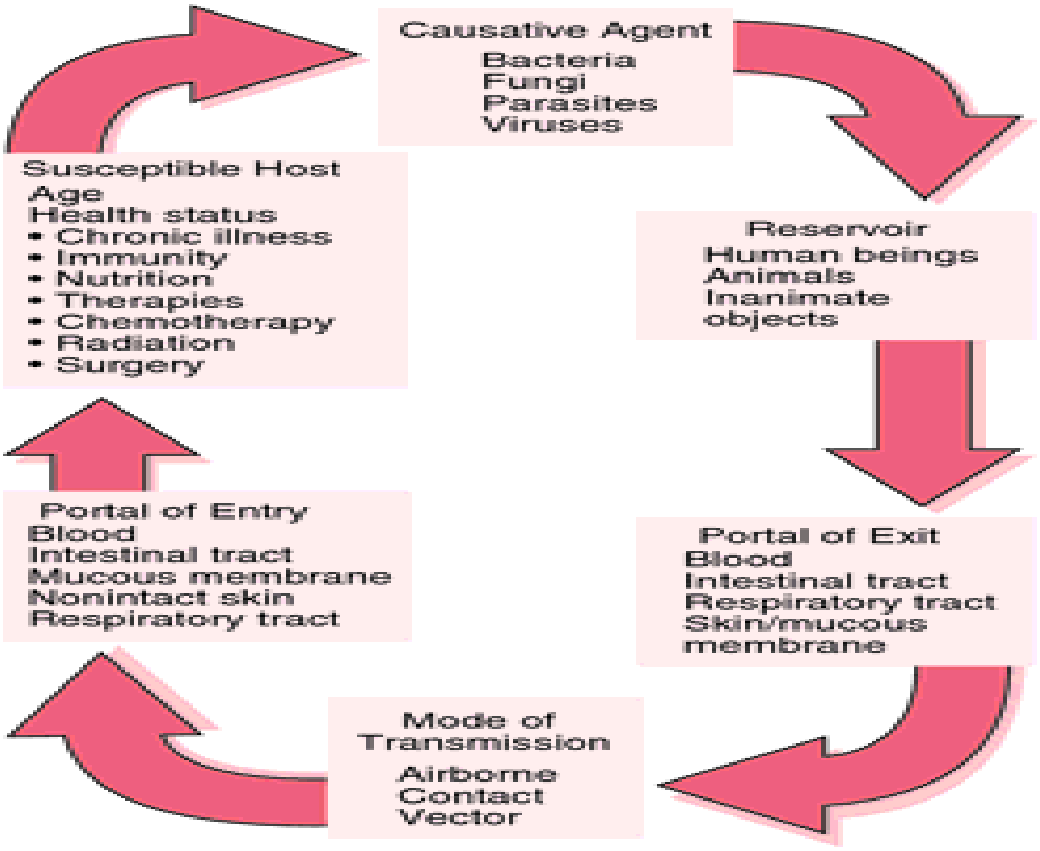

Figure 2.1 : Chain of infection, adopted from *Dorland's Medical Dictionary for Health Consumers*. (2007)

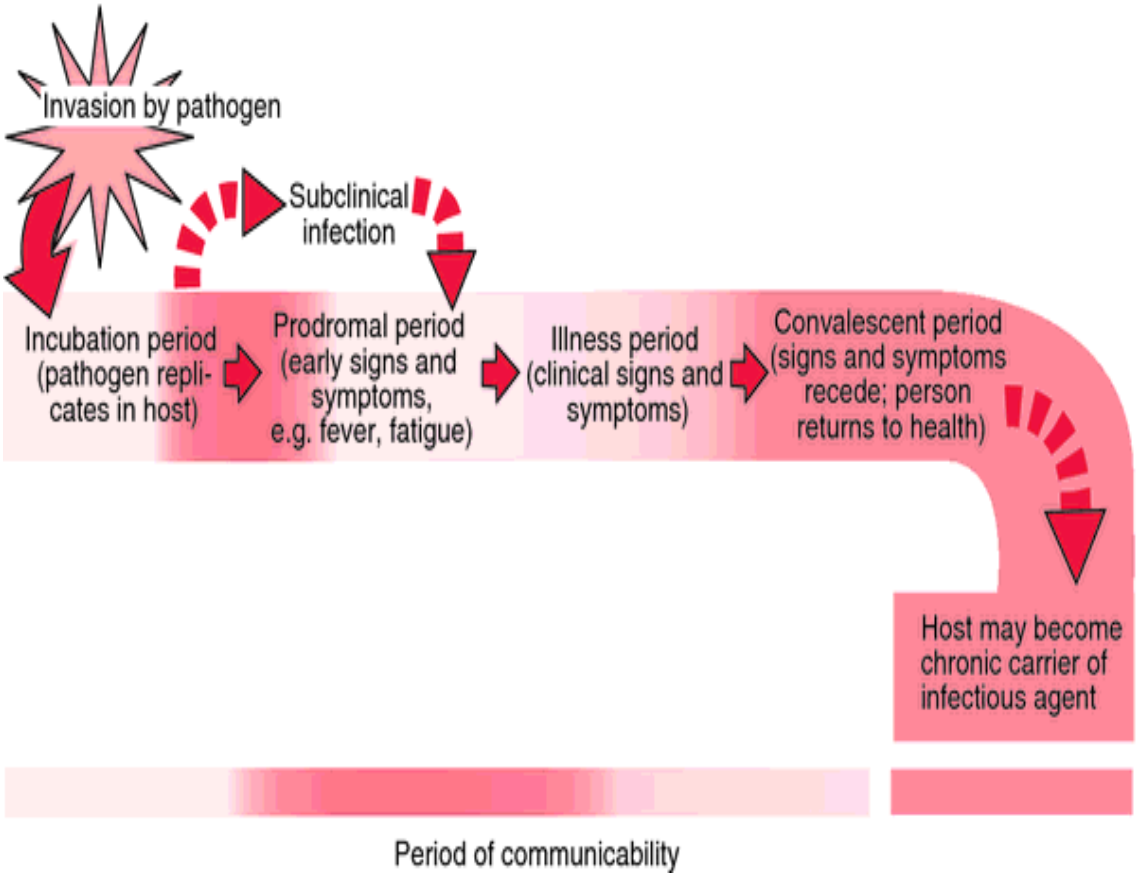

Figure 2.2 :

Stages of infection, each period varies with different pathogens and different diseases, adopted from *Dorland's Medical Dictionary for Health Consumers*. (2007)

2.2 SYSTEMIC INFLAMMATORY RESPONSE SYNDROME (SIRS)

Systemic inflammatory response to a variety of severe clinical insults. The response is manifested by two or more of the following signs (Bone *et al.*, 2009):

- A temperature >38 or <36^{o}C
- Heart rate >90 beats per minute
- Respiratory rate >20 breaths per minute or a PaCO2 <32 mmHg
- White blood cell count >12,000/mm^3 or<4000/mm^3, or the presence of >10% immature forms.

2.3 SEPSIS

The ACCP/ SCCM Consensus Conference Definitions (1992) defined sepsis is the systemic inflammatory response to infection, i.e. SIRS due to a presumed or identified site of infection. In association with infection, manifestations of sepsis are the same as those previously defined for SIRS. It is a clinical term used to define a patient who has symptomatic bacteremia, with or without organ dysfunction. It should be determined whether they are a direct systemic response to the presence of an infectious process and represent an acute modification from baseline in the absence of other known causes for such abnormalities (Bone *et al.*, 2009).

Dorland (2007) defined sepsis as the presence of pathogenic microorganisms or their toxins in the blood or other tissues.

Or in other words, infection together with the systemic manifestation of infection. A suspected or documented infection in the presence of the following is defined as sepsis :

- Temperature >38 or <36^{o}C
- Heart rate >90 beats per minute
- Tachypnoea : respiratory rate >20 breaths per minute or a PaCO2 <32 mmHg
- White blood cell count >12,000/mm^{3} or<4000/mm^{3}, or the presence of >10% immature forms.
- Altered mental status.
- Hyperglycemia (plasma glucose 140mg/dL or 7.7 mmol/L) in the absence of diabetes (Radford, 2013).

2.4 SEVERE SEPSIS

Severe sepsis is defined as sepsis associated with organ dysfunction, hypoperfusion or hypotension. Hypoperfusion and perfusion abnormalities may include but are not limited to lactic acidosis, oliguria or an acute alteration in mental status (Radford, 2013).

Sepsis-induced hypotension is defined as a systolic blood pressure <90 mmHg or mean arterial pressure <70 mmHg or decrease in SBP > 40mmHg below the normal for age in the absence of other causes of hypotension (Radford, 2013).

2.5 SEPTIC SHOCK

Septic shock is defined as sepsis associated with hypotension (systolic blood pressure < 90 mmHg, mean arterial pressure < 60 mmHg, or systemic blood pressure < 40 mmHg from baseline) despite satisfactory fluid resuscitation.

Septic shock is usually characterized by inadequate tissue perfusion and extensive cellular dysfunction. In contrast to other forms of shock (hypovolaemic, cardiogenic, or anaphylactic), cellular dysfuction in septic shock is not necessarily related to the hypoperfusion. Instead, there may be a metabolic block at the cellular level that contributes to impaired cellular oxidation (Morgan, 2006).

In simple sentences, septic shock is severe sepsis with hypotension after adequate fluid resuscitation (Bone *et al.*, 2009).

2.6 COMMUNITY-ACQUIRED INFECTION

Community-acquired infection is defined as infection derived from outside of a health care setting or an infection present on admission. It is often distinguished from hospital-acquired or nosocomial infection by the types of microorganisms that affect patients who are recovering from a disease or injury (*Mosby, 2009*). Community-acquired respiratory infections commonly involve strains of Haemophilus influenza or Streptococcus pneumonia and are usually more antibiotic sensitive.

2.7 HOSPITAL-ACQUIRED INFECTION

Hospital - acquired or nosocomial infections is defined as those occurring within 48 hours of hospital admission, 3 days of discharge or 30 days of an operation.

They affect 1 in 10 patients admitted to hospital. Approximately, a patient with hospital acquired infection spent 2.5-times longer in hospital, with additional costs more than an uninfected patient (Inweregbu *et al.*, 2005).

Intensive care units (ICU) have the highest incidence of hospital-acquired infections in the hospital setting. The European Prevalence of Infection in Intensive

Care Study (EPIC), involving over 4500 patients, demonstrated that the nosocomial infection prevalence rate in ICU was quite high, 20.6% (Inweregbu *et al.*, 2005).

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ICU patients are particularly at risk from nosocomial infections as a result of mechanical ventilation, use of invasive procedures and their immunocompromised status (Inweregbu *et al.*, 2005).

Gram-positive bacteria are the commonest source of nosocomial infections with *Staphylococcus aureus* being the predominant pathogen. However, gram-negative nosocomial infection was noted to be significantly increased in trend since 1986 (Weinstein *et al.*, 2005). The study showed that gram-negative bacilli continue to be associated with hospital-acquired infections in intensive care units (ICUs).

Weinstein *et al.* (2005) also stated that since 1970s, gram-negative bacilli constituted the majority of bacterial pathogens associated with the four major types of hospital-acquired infections :

1. **Nosocomial pneumonia**
    - Gram-negative aerobes continued the most commonly described bacterial pathogens associated with pneumonia in 2003 (65.9%), with the percentage of *Acinetobacter* species was significantly higher.

2. **Urinary tract infection (UTI)**

   - The most commonly reported gram-negative pathogens were *E.coli*, followed by *Pseudomonas aeruginosa*. However, the percentage of *Klebsiella pneumonia* and *Acinetobacter* isolates had increased significantly in the year of 2003.

3. **Surgical site infection (SSI)**

   - *Acinetobacter* isolates were more frequently reported.

4. **Primary blood-stream infection (BSI)**

   - Centers for Disease Control and Prevention (CDC) defined specifically, that primary bloodstream infection includes a laboratory-confirmed bloodstream infection and clinical sepsis. It must meet one of the following criteria :

     1. Recognized pathogen isolated from blood culture and pathogen is not related to infection at another site. OR

     2. One of the following: fever > 38 ^{o}C, chills, or hypotension AND any of the following:

        i. Common skin contaminant isolated from two blood cultures drawn on separate occasions AND the organism is not related to infection at another site **.

ii. Common skin contaminant isolated from blood culture from patient with intravascular access device, plus the physician introduces appropriate antimicrobial therapy

iii. Positive antigen test on blood and organism is not related to infection at another site (Digiovine *et al.*, 1999).

3. Patient < 12 months of age has one of the following : fever > 38 ^{o}C, hypothermia (<37^{o} C), bradycardia or apnea, and any of the following :

    i. Common skin contaminant isolated from two blood cultures drawn on separate occasions and organism is not related to infection at another site **.

    ii. Common skin contaminant isolated from blood culture from patient with intravascular access device, and physician institutes appropriate antimicrobial therapy.

    iii. Positive antigen test on blood and pathogen is not related to infection at another site (Garner *et al.*, 1988).

** when an organism isolated from blood culture is compatible with an associated nosocomial infection at another site, the blood - stream infection is categorized as a secondary blood stream - infection. Exceptions to this are intravascular device – associated blood stream infections, all of which are categorized as primary if localized signs of infection are present at the access site (Garner *et al.*, 1988)

There has been a growth in the degree of antibiotic resistant bacteria associated with nosocomial infections in ICU. Bacteria develop resistance when they acquire new genetic material. Poor antibiotic prescribing selects for resistant bacteria.

This highlights the need for the use of appropriate and adequate antibiotics because inadequate antibiotic therapy is associated with poor outcome and emergence of bacterial resistance.

Factors that predispose to nosocomial infections: Adopted from The European Prevalence of Infection in Intensive Care Study (EPIC); adopted from (Inweregbu *et al.*, 2005) :

1) Related to underlying health status
    - Advanced age
    - Malnutrition
    - Alcoholism
    - Heavy smoking
    - Chronic lung disease
    - Diabetes

2) Related to acute disease process
    - Surgery
    - Trauma
    - Burns

3) Related to invasive procedures
    - Endotracheal or nasal intubation
    - Central venous catheterisation
    - Extracorporeal renal support
    - Surgical drains
    - Nasogastric tube
    - Tracheostomy
    - Urinary catheter

4) Related to treatment

- Blood transfusion
- Recent antimicrobial therapy
- Immunosuppressive treatments
- Stress-ulcer prophylaxis
- Recumbent position
- Parenteral nutrition
- Length of stay

2.7.1 BLOOD-STREAM INFECTION

Bloodstream infection (BSI) is the most frequent and common infection in critically ill patients. As blood - stream infections among patients in intensive care units (ICU's) are usually secondary to intravascular catheters, they can be triggered by both Gram-positive and Gram-negative microorganisms as well as fungi. Infection with multidrug - resistant (MDR) organisms is becoming more frequent and common, making the choice of empirical antimicrobial therapy more challenging.

Karchmer (2000) stated that, clinical bloodstream infections (BSIs), which characterize the failure of the immune system to surround infection at a focal site and resulting disseminated disease, are a major reason of morbidity and mortality.

The rate of these infections, their epidemiology, and the invading organisms have changed in parallel with the expansion of medical care, predominantly with the development of an ever more ill and immunocompromised population of hospitalized patients who are often seriously dependent on medical support and indwelling devices.

Currently more than 50% of blood - stream infections are hospital acquired and it is estimated that hospitalized patients in the United States have 250,000 episodes of nosocomial blood - stream infections yearly, and when these infections occur in patients in intensive care units, they are associated with an attributable mortality rate of 35%, 24% additional hospital days, and extra hospital costs of $40,000 per survivor (Karchmer, 2000).

2.7.1.1 GRAM-POSITIVE BACTEREMIA :

The incidence of Gram-positive bloodstream infections also has been increasing progressively. Currently, the 3 most common causes of nosocomial blood-stream infections in the United States are coagulase-negative staphylococci, *Staphylococcus aureus*, and *Enterococci spp.* (Karchmer, 2000).

The virulence of coagulase-negative staphylococci is based mostly on their capability to produce biofilms, and thus cause infections of intravascular devices and foreign bodies, which must be removed to resolve the infection. *Staphylococcus aureus* is the leading cause of endocarditis, and it is important to recognize patients at risk of

the complications of *Staphylococcus aureus* bloodstream infections. *Enterococci* spp. are the third leading cause of Gram-positive bacteraemia in our institution. Management of this disease is difficult because of its intrinsic resistance to antibiotics, mainly in *Enterococcus faecium* infections (Karchmer, 2000).

The recently defined synergism of ampicillin plus ceftriaxone is a good therapeutic option for *Enterococcus faecalis* bacteraemia and endocarditis produced by high-level aminoglycoside-resistant strains (Karchmer, 2000).

Nosocomial bacteremia caused by viridans streptococci and *S. aureus* occurs prior during hospitalization than does bacteremia caused by gram-negative bacilli, *Candida*, and enterococci. The average time to commencement of bacteremia caused by streptococci and *S. aureus* is ~2 weeks after the start of hospitalization. Gram-negative bacilli, *Candida*, and enterococci are encountered in blood cultures on average a week or so longer after the start of hospitalization. The mean period to onset of bacteremia caused by coagulase-negative staphylococci is ~19 days after the start of hospitalization (Rello, 1999).

Organisms producing nosocomial blood - stream infections differ depending on the site of patients within the institution. Coagulase-negative staphylococci are more likely to be isolated from cultures of blood specimens from patients in intensive care settings, while viridans streptococci and *Staphylococcus aureus* are more frequently isolated from ward patients. Enterococci are isolated with similar frequency from

patients in both settings. Blood - stream infections caused by viridans streptococci are associated with neutropenia and are commonly detected in patients on the hematology and oncology services. Crude mortality rates among patients with blood - stream infections caused by these gram-positive cocci range from 17% to 32%, the lowest mortality rates are associated with coagulase-negative staphylococci, and the highest mortality rates have been presented among patients with enterococcal bacteremia (Pittet *et al.*, 1994).

2.7.1.2 GRAM-NEGATIVE BACTEREMIA :

Gram-negative bacteremia was defined as the isolation of gram-negative bacilli in a blood culture specimen. Orsini *et al.* (2012) stated that the most common Gram-negative bacteria isolated from blood culture were *Klebsiella spp* with 80% of *Klebsiella pneumonia*, followed by *Acinetobacter baumannii* and *E. coli* . Kang *et al.* (2011) stated gram-negative bacilli such as *Enterobactericeae* and *Pseudomonas aeruginosa* are the prominent causes of nosocomial blood stream infections. Among the gram-negative bacilli, antibiotic-resistant strains have been emerged dramatically and are being increasingly concerned.

The most common ESBL-producers were *Klebsiella pneumoniae* and *Acinetobacter baumannii*, where as Carbapenem-resistant phenotype were *Klebsiella pneumoniae, Acinetobacter baumannii* and *Pseudomonas aeruginosa.* The most common risk factors for MDR infections were diabetes mellitus and malignancy.

The epidemiology of microorganisms producing blood stream infections radically changed over years, with a simultaneous increase in antimicrobial resistance. A nationwide surveillance study directed in 49 hospitals in USA showed a large prevalence of Gram-positive bacteria causing blood - stream infection compared with Gram-negative organisms. However, a trend towards an increasing incidence of Gram-negative organisms causing blood - stream infections has been observed more in recent times (Orsini *et al.*, 2012).

2.7.1.3 FUNGI :

Candida albicans blood - stream infections are the most common invasive fungal infections among hospitalized patients. In the USA, it is currently the fourth prominent cause of nosocomial blood - stream infections among hospitalized patients and third among ICU patients. The incidence and epidemiology of invasive candidiasis in the ICU's has undergone significant change in the past decades. Significant regional and geographic variations exist in the incidence of the different Candida species. Kett *et al.* (2011) reported *Candida albicans* as the most common Candida species isolated among patients in ICU's [(Wisplinghoff *et al.*, 2004), (Kett *et al.*, 2011).

In some series, non-albicans species account for almost half of all Candida blood - stream infections. *Candida glabrata* is generally the second most commonly isolated pathogen in North America [(Wisplinghoff *et al.*, 2004, (Horn *et al.*, 2009).

Retrospective cohort studies have been commenced to approximate mortality attributable to candidemia and report rates ranging from 10% to 49%, with increase in the hospital costs. The gold standard diagnostic test for invasive candidiasis has been isolation of the organism by blood culture. Detection of candidemia by blood culture often takes more than 24 hours. For certain species, such as *Candida glabrata*, the time can be even longer, leading to a significant delay in appropriate therapy and higher mortality (Posteraro *et al.*, 2011).

2.8 MULTIDRUG RESISTANT GRAM-NEGATIVE BACILLI

Development of resistance to multiple antimicrobial agents in pathogenic bacteria has become a significant public health risk as there are fewer, or even sometimes no effective antimicrobial agents obtainable for infections produced by these bacteria. Gram-positive and Gram-negative bacteria are both affected by the development and rise of antimicrobial resistance.

Multidrug resistant in gram-negative organisms was defined as resistance to at least one antimicrobial in three or more antimicrobials classes: aminoglycosides, third generation cephalosporins, fluoroquinolones, and carbapenems, including organisms with Extended-Spectrum β-Lactamases (ESBL's), and Carbapenem-Resistant Enterobacteriaceae (CRE). Among the Gram-positive organisms, multidrug resistant was defined as methicillin resistance in *Staphylococcus aureus* and vancomycin resistance in *Enterococcus species* (Orsini *et al.*, 2012).

2.8.1 DRUG – RESISTANCE DEFINITIONS

According to Magiorakos *et al.* (2012), the resistance characteristic of microorganisms is categorized into:

- multidrug-resistant (MDR) is defined as non-susceptibility to at least one agent in three or more antimicrobial categories.

- extensively drug-resistant (XDR) is defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories (i.e. bacterial isolates remain susceptible to only one or two categories).

- pandrug-resistant (PDR) is defined as non-susceptibility to all agents in all antimicrobial categories (i.e. no agents tested as susceptible for that organism).

Therefore, a bacterial isolate that is categorized as entensively drug – resistant (XDR) will also be categorized as multi drug - resistant (MDR). Equally, a bacterial isolate would have to be extensively drug - resistant (XDR) in order for it to be further defined as pandrug - resistant (PDR).